While private involvement in genome research may not, in itself, be controversial, scientists are concerned about whether pieces of DNA sequenced under private auspices would remain in the public domain. At Collaborative, the answer is that DNA sequenced with public money would be in the public domain. But DNA sequenced under contract for pharmaceutical companies would remain private.

For Collaborative, the profit would lie in two areas. In its reference lab, the company has an immediate outlet for genetic tests. And Collaborative would receive royalties on new drugs devel-

oped from DNA pieces it sequenced or mapped for drug companies.

Scientists believe this is the approach that Bourke would take as well. Craig Venter of NIH's National Institute of Neurological Disorders and Stroke (Bethesda, MD) says that he considered joining Bourke. Venter recently raised hackles in the research community over NIH's move to patent more than 300 human genes that he sequenced, one of the largest chunk of DNA for which a patent had been filed. With Bourke, Venter asked that any base pairs sequenced be made publicly available, as they would be if sequenced at NIH.

"Bourke agreed to that immediately," Venter says.

Venter turned Bourke down, he says, "not because of any negative aspects" of the entrepreneur's plans, but because such a move would "exacerbate the questions over NIH patenting." But he hopes Bourke is able to form a company. "The science is changing more rapidly than the official leaders of the genome project are ready for," Venter says. If the human genome is ever to be sequenced, he adds, "a large company or large government enterprise would be the most efficient way to do it."

—Mimi Bluestone

NEW STUDY, OLD RESULTS

t-PA FALLS SHORT ONCE AGAIN

NEW YORK—The news for thrombolytic agents was good, but the news for genetically engineered thrombolytics was bad. The results of the Third International Study of Infarct Survival (ISIS-3) showed alteplase—Burrhoughs Wellcome's (Research Triangle Park, NC) recombinant tissue plasminogen activator (t-PA)—in a dead heat as far as efficacy with Astra Pharmaceutical's (Westborough, MA) microbial streptokinase (SK) and SmithKline Beecham's (Philadelphia, PA) recombinant anistreplase (APSAC).

The study of more than 40,000 patients in 20 countries showed that mortality for patients receiving t-PA was 10.3 percent, compared with 10.5 percent for APSAC and 10.6 percent for SK. "The bottom line is that utilization of these agents would save lives," said Charles Hennekens, professor of preventive medicine at Harvard Medical School (Cambridge, MA), who coordinated U.S. participation in the study.

t-PA costs seven times more

But in an era of cost-conscious medicine, SK showed it could save lives for less money: SK costs \$300 a treatment, compared with \$1,700 for APSAC and \$2,200 for t-PA. And SK provided another benefit: fewer strokes due to cerebral hemorrhage. In the ISIS-3 study, patients receiving SK suffered 3 strokes for every 1,000 patients, compared with six in 1,000 among patients given APSAC and seven in 1,000 for those given t-PA. Compared with SK and APSAC, though, t-PA was associated with fewer reports of allergy and hypotension requiring drug treatment. The results of ISIS-3, which was coordinated at Oxford University in the U.K., were similar to those of an earlier study coordinated in Milan, Italy, the GISSI study.

Harvard's Hennekens says that he and other researchers had hoped that t-PA's

high specificity for fibrin and its speedy work as a clot-buster would translate into lower mortality. But, he says, "it may be it's not so much the speed of reperfusion but whether reperfusion occurs at all."

SK, APSAC, and t-PA all have their place, Hennekens believes. For a patient who has previously received SK, he would "demand" t-PA to avoid the possibility of anaphylactic reaction from a second exposure to the microbial product. APSAC, for its part, "seems like a particularly promising agent," Hennekens says, because it can be given within minutes as a bolus injection, say, in an ambulance, unlike SK and t-PA, which require infusion for more than an hour.

Currently, the only producer of t-PA is Genentech (S. San Francisco, CA), which makes alteplase. As far as Wellcome's alteplase, a 1990 injunction based on a patent infringement ruling that year prevents Wellcome from marketing the product. Wellcome says the patent decision, plus efficacy data from the GISSI study, convinced it to abandon further development of alteplase and of a second-generation t-PA produced for it by Genetics Institute (Cambridge, MA).

Genentech yells foul

For its part, Genentech maintains that extrapolating stroke data for alteplase to alteplase is inappropriate, because alteplase is a double-chain molecule while alteplase is a single-chain compound. In a Genentech-sponsored study now underway in 600 U.S. hospitals, data on 17,000 patients treated with alteplase show a stroke rate "well below the rate reported in ISIS-3 for alteplase," says a Genentech spokesman. The Genentech study is called the National Registry for Myocardial Infarction.

But Genentech could not say how the two versions of t-PA might differ in efficacy. "There's never been a head to head comparison," the spokesman says.

Hennekens says that Genentech's European distributors refused to provide t-PA for ISIS-3. That led investigators in Europe, he says, to quip that Genentech's complaint that its drug was not used was "like a child who killed both parents and appealed for clemency on the basis that it was an orphan." The Genentech spokesman insists that the company was never asked to provide t-PA for ISIS-3.

In the ISIS-3 study, half the patients in each thrombolytic category received the anti-coagulant heparin subcutaneously. For this reason, Genentech questions the relevance of the results to the U.S., where heparin is typically administered intravenously with alteplase. An international study now underway, the Global Utilization of Streptokinase and t-PA in Occluded Coronary Arteries (GUSTO), will compare SK and alteplase in patients who are given intravenous heparin.

There's some evidence that Genentech is already paying for the high cost of alteplase. A study sponsored by Astra Pharmaceutical showed that 22 percent of 400 U.S. cardiologists surveyed have changed their choice of thrombolytics in favor of SK and that 43 percent are considering such a change. According to the survey, 56 percent of cardiologists still use t-PA on a regular basis.

Genentech says that any market shift away from t-PA occurred last year and that its market share is now "stable" at 53 percent of U.S. patients who receive thrombolytic therapy, compared with 36 percent who receive SK and 11 percent who get APSAC. Genentech says that it has no plans to lower the cost of its t-PA.

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